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An Invert U-Shaped Curve: Relationship Between Fasting Plasma Glucose and Serum Uric Acid Concentration in a Large Health Check-Up Population in China

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Abstract: There are some published studies focus on the invert U-shaped relationship between fasting plasma glucose (FPG) and serum uric acid (UA), while the threshold value and gender differences of this relationship were still obscure. We aimed to explore the dose–response relation between FPG level and serum UA concentration by conducted this epidemiological research in a large health check-up population in China.

A total of 237,703 people were collected from January 2011 to July 2014 in our cross-sectional study; 100,348 subjects age 18 to 89 years and without known diabetes were included for the current analysis. One-way analysis of variance, generalized additive models, and 2-piecewise linear regression model were used.

The mean concentration of UA with FPG of <6.1, 6.1 to 6.9, and ≥7.0 mmol/L was 240.9, 260.2, and 259.6 μmol/L in women and 349.0, 360.8, and 331.0 μmol/L in men. An invert U-shape with a threshold FPG of 7.5 (women)/6.5 (men) mmol/L was observed in the regression curve of FPG and UA, even after adjusting for potential confounders. The adjusted regression coefficients were 2.4 (95% confidence interval [CI]: 1.5 to 3.4, $P < 0.001$) for FPG < 7.5 mmol/L, −3.2 (95% CI: −5.0 to −1.3, $P < 0.001$) for FPG ≥ 7.5 mmol/L in women; while 0.8 (95% CI: −0.4 to 2.0, $P = 0.19$) for FPG < 6.5 mmol/L, −7.1 (95% CI: −8.0 to −6.1, $P < 0.001$) for FPG ≥ 6.5 mmol/L in men. Furthermore, the interaction between different FPG level and sex was significant ($P < 0.05$).

An invert U-shape with a threshold of FPG was existed for serum UA level in Chinese adults age 18 to 89 years without known diabetes, and significant gender differences were found. Future researches should pay more attention to this relationship.

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Abbreviations: BMI = body mass index, CHD = coronary heart disease, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HUA = hyperuricemia, IFG = impaired fasting glucose, OGTT = oral glucose tolerance test, SBP = systolic blood pressure, SCr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid.

INTRODUCTION

Serum uric acid (UA), the final product of purine metabolism in humans with the loss of uricase, is a strong predictor of stroke in patients with noninsulin-dependent diabetes mellitus,[1] and hyperuricemia (HUA) is a significant and independent factor which predicts poor outcome following stroke in patients with diabetes.[2] Despite the fact that both HUA and diabetes can increase the risk of stroke,[1,3,4] chronic kidney disease (CKD),[5,6] and coronary heart disease,[7–9] their interrelationship requires clear definition before examining their roles in those diseases.

Many researches showed that overt diabetes was associated with low UA level, particularly in diabetic men.[10–17] A prospective study[16] among 10,000 men reported that the serum UA levels were higher in prediabetics than in nondiabetics, but decreased in stage of diabetes. Similarly, an invert U-shaped relationship between fasting plasma glucose (FPG) and UA was found in a general Chinese population with higher serum UA concentration.[14] Nevertheless, the threshold value of this relationship remains unclear. On the other hand, not all studies have come to the coincident conclusion,[18,19] and gender differences were also presented.[20] Recently, a research[20] reported that the UA level and the incidence of HUA tended to increase along with the increasing level of FPG in middle-aged and elderly Chinese women and the increasing FPG might also increase the risk of HUA, but not in men.

In order to investigate the precise dose–response relation between FPG level and serum UA concentration, we conducted a cross-sectional study among a large health check-up population in China. Our primary goals were to answer the following questions: Is the FPG level invert U-shaped related to serum UA in women and men without prior history of diabetes? If such a relationship exists, what is the threshold value? Does it differ significantly between the 2 genders?

MATERIALS AND METHODS

Study Site

The study setting is in Wuhu city, Anhui province, China. The city located at the confluence of the Qingyi River and Yangtze River (center coordinates: 118°38 east longitude and 31°33 north latitude). There are more than 3 million residents and 4 districts (Jinghu, Jiujiang, Yijiang, and Sanshan) and 4 counties (Wuhu, Nanling, Fanchang, and Wuwei). With the rapid economic development in recent years, the residents' health consciousness is increasing.

Study Subjects and Sample Collection

A total of 237,703 Chinese people age 18 to 89 years who received the physical examination in the Physical Examination Center of the First Affiliated Hospital of Wannan Medical College from January 2011 to July 2014 were collected. In this study, inclusion criteria included: age 18 to 89 years, underwent both FPG and serum UA check. Exclusion criteria included: no available data on age, sex, height, weight, FPG, UA, smoking, drinking, systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), and serum creatinine (SCr); those taking antihypertensive or antidiabetic agents, lipid-lowering, or hypouricemic agents; participants with self-reported prior history of diabetes, rheumatologic or renal disease, stroke, cancer, gout; and duplicate cases. After the subjects with incomplete data (n = 49,102) were removed and duplicate cases (n = 72,604) were deleted, there were 115,997 people left. Individuals with known prior history of mentioned diseases or taking mentioned medicine (n = 15,649) were also excluded. Subjects without known diabetes but with FPG > 7.0 mmol/L in this examination (newly diagnosed diabetes, n = 2973) were included. Finally, 100,348 (55,535 men, 55.3%) subjects age 18 to 89 years with the required information were included in the analysis.

According to local and international guidelines on ethics considerations in research involving human participants, this study was approved by the Ethics Committee of Wannan Medical College. Verbal informed consent was obtained from each subject before participation in this study after all procedures had been explained. Data related to individual identification were removed and remained anonymous during the entire analysis.

Recorded contents: general data including age and gender; medical history including the history of diabetes, rheumatologic or renal disease, stroke, cancer, gout, etc.; physical examination (the height [cm], body weight [kg], and blood pressure [mm Hg] were measured and recorded); and biochemical indicators including TC, TG, HDL-C, FPG, UA, and SCr. The subjects were advised to have an overnight fast for above 12 h, and 5 mL venous blood sample was collected from each subject. Then the blood sample was determined in the clinical laboratory by enzyme-coupled spectrophotometric assay, oxidase method or turbidity method with Hitachi 7600 automatic biochemical analyzer.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation[21]:

$$\text{eGFR} = 141 \times \min(\text{SCr}/k, 1)^{\alpha} \times \max(\text{SCr}/k, 1)^{-1.209}$$
$$\times 0.993^{\text{Age}} \times 1.018 \quad [\text{if female}]$$

where SCr is expressed in mg/dL (if expressed in l μmol/L, divided by 88.4) and age in years; k: 0.7 for women and 0.9 for men; α: −0.329 for women and −0.411 for men; min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

Statistical Analysis

Before analysis, FPG was expressed as mmol/L and serum concentration of UA was expressed as μmol/L. Means (standard deviation) or medians (25th percentile, 75th percentile) and proportions were calculated for characteristics according to FPG categories. The total TG and SCr levels were positively skewed and thus natural log-transformed to normalize their distribution. The analysis of variance for continuous variables and chi-squared test for categorical variables were applied to compare the characteristics of the study subjects between FPG categories. The Kruskal–Wallis rank-sum test was also used to compare the TG and SCr levels between FPG categories.

In addition, we explored the possible nonlinear relationship between FPG and UA by using generalized smoothing splines with knot locations generated automatically in generalized additive models[22] by R package mgcv. We further applied a 2-piecewise linear regression model to examine the threshold effect of the FPG on UA. The threshold level (i.e., turning point) was determined by using trial and error, including selection of turning points along a predefined interval and then choosing the turning point that gave the maximum model likelihood. Meanwhile, we applied linear regression analyses to estimate the relationship between FPG and UA concentration within each stratum of FPG with or without adjustment for potential confounders, and Wald χ^2 test was used to test the effect between strata. All P values were 2-tailed, with a significance level of 0.05. Data management and all analyses were performed using R software program, version 3.0.0 (http://www.R-project.org).

RESULTS

Subject Characteristics

The serum UA level was significantly higher in men than in women (349.2 ± 73.7 vs 242.2 ± 57.4 μmol/L, $P < 0.001$). The HUA prevalence of the study population was 10.8% and men significantly higher than women (16.7% vs 3.5%, $P < 0.001$). The prevalence rates of newly diagnosed diabetes (FPG of ≥7.0 mmol/L) and impaired fasting glucose (IFG, FPG of 6.1–6.9 mmol/L) were 3.0% and 6.3%, respectively, and greater for men than women (3.9%, 7.6% vs 1.8%, 4.5%, respectively).

In general, compared with individuals with FPG of <6.1 mmol/L, participants with IFG or newly diagnosed diabetes were older, more obese, and more likely to have higher SBP/DBP, FPG, TG, TC, SCr levels, and lower HDL-C in either men or women ($P < 0.05$). Individuals with IFG had the highest serum UA level and those with FPG of <6.1 mmol/L had the lowest UA level in women. Instead, individuals with newly diagnosed diabetes had the lowest serum UA level and those with IFG had the highest UA level in men. Participants with newly diagnosed diabetes had the highest rates of regular smoking and drinking among 3 FPG groups for men. Smoking and drinking rates were relatively rare (0.2–0.4%) in women (Table 1).

Sex-Specific Analysis of the Relationship Between FPG and UA

Because of the different characteristics between women and men, we perform the analysis in stratifying participants by sex. Generalized smoothing splines suggest that an invert U-shape with a threshold glucose of 7.5 (women)/6.5 (men) mmol/L was observed between the FPG and serum UA concentration (Figure 1A–D). The threshold effect of FPG on UA level was also significant after adjusting for various potential confounders, although the regression coefficients have been reduced in some of the models as shown in Table 2. The adjusted regression coefficient was 2.4 (95% confidence interval [CI]: 1.5–3.4, $P < 0.001$) for FPG < 7.5 mmol/L while −3.2 (95% CI: −5.0 to −1.3, $P < 0.001$) for FPG ≥ 7.5 mmol/L in women,

TABLE 1. Characteristics of the Study Population by FPG Categories and by Gender in a Large Health Check-Up Chinese Population Without Known Diabetes in 2011 to 2014 in Wuhu

	Women				Men			
	FPG < 6.1 mmol/L	FPG = 6.1–7.0 mmol/L	FPG ≥ 7.0 mmol/L	P Value	FPG < 6.1 mmol/L	FPG = 6.1–7.0 mmol/L	FPG ≥ 7.0 mmol/L	P Value
N	41,962	2038	813		49,132	4243	2160	
Age, y	40.8 ± 12.1	50.4 ± 11.4	53.6 ± 11.0	<0.001	41.1 ± 12.4	48.1 ± 11.7	50.1 ± 10.9	<0.001
BMI, kg/m^2	22.4 ± 3.0	24.2 ± 3.3	24.9 ± 3.4	<0.001	24.1 ± 3.1	25.4 ± 3.1	25.7 ± 3.1	<0.001
DBP, mm Hg	73.1 ± 8.6	77.8 ± 9.1	78.3 ± 9.2	<0.001	79.1 ± 9.4	83.0 ± 9.8	83.7 ± 10.1	<0.001
SBP, mm Hg	110.7 ± 14.1	121.0 ± 15.8	124.5 ± 17.5	<0.001	118.1 ± 14.5	125.5 ± 15.9	127.3 ± 16.7	<0.001
FPG, mmol/L	5.1 ± 0.4	6.4 ± 0.2	9.1 ± 2.9	<0.001	5.2 ± 0.4	6.4 ± 0.2	9.3 ± 2.8	<0.001
HDL, mmol/L	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	<0.001	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	<0.001
TC, mmol/L	4.5 ± 0.8	4.9 ± 0.9	5.1 ± 1.0	<0.001	4.6 ± 0.9	5.0 ± 0.9	5.1 ± 1.0	<0.001
TG, mmol/L	1.0 (0.7–1.4)	1.2 (0.9–1.8)	1.5 (1.1–2.1)	<0.001	1.3 (0.9–2.0)	1.7 (1.1–2.5)	1.9 (1.3–3.0)	<0.001
UA, μmol/L	240.9 ± 56.6	260.2 ± 64.5	259.6 ± 70.2	<0.001	349.0 ± 72.8	360.8 ± 77.9	331.0 ± 80.6	<0.001
SCr, μmol/L	55.6 (50.1–61.4)	56.1 (50.5–62.3)	53.7 (47.2–60.6)	<0.001	78.3 (71.3–85.6)	78.0 (70.6–85.5)	73.6 (65.7–81.9)	<0.001
eGFR, mL/min/1.73m^2	111.0 ± 13.8	103.0 ± 13.8	102.9 ± 14.6	<0.001	104.4 ± 13.8	99.6 ± 13.5	101.4 ± 13.9	<0.001
Smoking status, N (%)				0.82				<0.001
Never	41,767 (99.5%)	2028 (99.5%)	811 (99.8%)		23,708 (48.3%)	2221 (52.3%)	981 (45.4%)	
Marginal	44 (0.1%)	2 (0.1%)	0 (0.0%)		3782 (7.7%)	306 (7.2%)	132 (6.1%)	
Occasional	17 (0.0%)	2 (0.1%)	0 (0.0%)		1402 (2.9%)	76 (1.8%)	35 (1.6%)	
Regular	134 (0.3%)	6 (0.3%)	2 (0.2%)		20,240 (41.2%)	1640 (38.7%)	1012 (46.9%)	
Drinking status, N (%)				0.07				<0.001
Never	40,900 (97.5%)	1973 (96.8%)	786 (96.7%)		19,735 (40.2%)	1475 (34.8%)	774 (35.8%)	
Marginal	445 (1.1%)	27 (1.3%)	17 (2.1%)		15,349 (31.2%)	1356 (32.0%)	662 (30.6%)	
Occasional	491 (1.2%)	29 (1.4%)	8 (1.0%)		3547 (7.2%)	206 (4.9%)	83 (3.8%)	
Regular	126 (0.3%)	9 (0.4%)	2 (0.2%)		10,501 (21.4%)	1206 (28.4%)	641 (29.7%)	

Data are presented as mean ± standard deviation, median (25th percentile, 75th percentile), or number of subjects (%).
BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, SBP = systolic blood pressure, SCr = serum creatinine, TC = total cholesterol, TG = triglycerides, UA = uric acid.
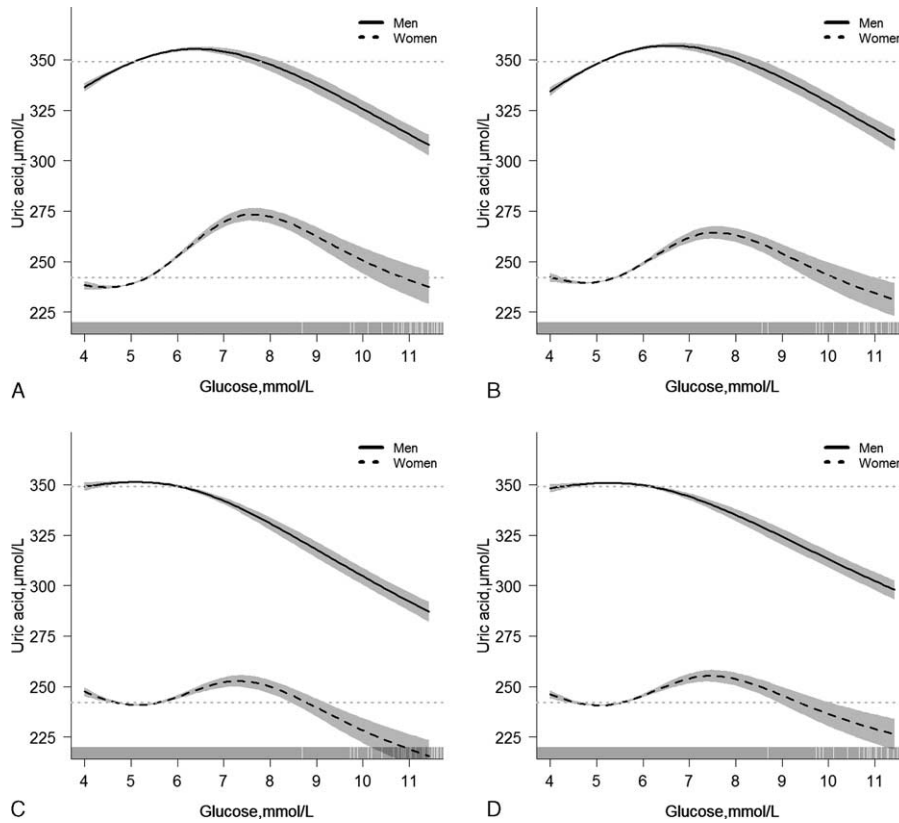
FIGURE 1. Relationship between fasting plasma glucose (mmol/L) and serum uric acid concentration (μmol/L) and their 95% confidence intervals (shade scope) in men (solid line) and women (dashed line) in individuals without known diabetes, which using generalized smoothing splines with 5 knots. Two horizontal thin dashed lines represent mean serum uric acid of men (higher) and women (lower), respectively. An invert U-shape with a threshold glucose of 7.5 (women)/6.5 (men) mmol/L was observed between the fasting plasma glucose and serum uric acid concentration, even after adjusting for confounding factors. Fasting plasma glucose was limited to 0.5% to 99.5%, each vertical rug line on the figure represents a subject. (A) No adjustment; (B) adjustment for age; (C) additional adjustment for body mass index, diastolic blood pressure, systolic blood pressure, total cholesterol, triglycerides, drinking status, smoking status, and antihypertensive treatment status; and (D) further adjustment for estimated glomerular filtration rate.

and the difference between 2 stratums was 6.2 (95% CI: 4.4–7.9, $P < 0.001$). Additionally, the adjusted regression coefficient was 0.8 (95% CI: −0.4 to 2.0, $P = 0.19$) for FPG < 6.5 mmol/L while −7.1 (95% CI: −8.0 to −6.1, $P < 0.001$) for FPG ≥ 6.5 mmol/L in men, and the difference between 2 stratums was 8.6 (95% CI: 7.2–10.1, $P < 0.001$; Table 2; Figure 2).

Compare Genders Difference of the Relationship Between FPG and UA

Furthermore, for participants with FPG < 7.5 mmol/L in women and FPG < 6.5 mmol/L in men, the difference between 2 genders was 1.0 (95% CI: −0.5 to 2.5, $P = 0.21$). On the other hand, the difference between 2 genders in participants with FPG ≥ 7.5 mmol/L in women and FPG ≥ 6.5 mmol/L in men was 3.7 (95% CI: 1.6–5.8, $P < 0.001$). Similar results were obtained in stratified according to the traditional standard (7.0 mmol/L; Table 2; Figure 2).

DISCUSSION

In our present study, we found an invert U-shape with a threshold glucose of 7.5 (women)/6.5 (men) mmol/L in the regression curve of FPG and serum UA in individuals without

prior history of diabetes. For participants with FPG ≥ 7.5 mmol/L in women and FPG ≥ 6.5 mmol/L in men, the downward slope of relationship between FPG and serum UA in man was higher than that of woman (Table 2).

Many studies have demonstrated that serum UA is significantly elevated with increasing of FPG level in nondiabetic stage, and reduced after the onset of diabetes.[11–14,17,23] The British Regional Heart Study[17] revealed that there was a positive relationship between serum glucose and serum UA when serum glucose concentration was <8.0 mmol/L, however, with higher level of glucose, the serum UA decreased. Likewise, Whitehead et al[11] found that the inflection point values of glucose were 9.0 mmol/L in women and 7.0 mmol/L in men. In addition, Hairong et al[13] and Nan et al[13,14] conducted 2 population-based surveys among Chinese adults in Qingdao, China, and they found that the inflection point value of glucose was 7.0 mmol/L. Therefore, UA may serve as a potential biomarker of deterioration in glucose metabolism. Our present study confirmed the previous findings and further explored the difference between genders in a large sample size. In women, although participants with IFG and newly diagnosed diabetes had higher serum UA level, there was a decreasing trend in serum UA concentration with the level of FPG increased when the FPG more than 7.5 mmol/L.

TABLE 2. Linear Regression Model for Serum UA Concentration (μmol/L) in Relation to FPG Concentration (mmol/L), the Models Were Made Separately for Different FPG Stratified in Individuals Without Known Diabetes

Glucose Group, mmol/L	N	Uric acid, μmol/L	Crude[†] β	SE	P	Model 1[‡] β	SE	P	Model 2[§] β	SE	P	Model 3[∥] β	SE	P
Women														
Stratum 1[*]														
<7.5	44,262	242.0 ± 57.2	10.7	0.5	<0.001	6.6	0.5	<0.001	1.4	0.5	0.007	2.4	0.5	<0.001
≥7.5	551	255.9 ± 72.4	−4.6	1.0	<0.001	−4.4	1.0	<0.001	−4.8	0.9	<0.001	−3.2	0.9	<0.001
Difference between 2 stratums			15.2	0.9	<0.001	11.0	0.9	<0.001	6.6	0.9	<0.001	6.2	0.9	<0.001
Stratum 2														
<7.0	44,000	241.8 ± 57.1	10.5	0.5	<0.001	6.4	0.6	<0.001	1.2	0.5	0.02	2.2	0.5	<0.001
≥7.0	813	259.6 ± 70.2	−4.4	0.8	<0.001	−4.4	0.8	<0.001	−4.8	0.8	<0.001	−3.3	0.8	<0.001
Difference between 2 stratums			15.0	0.9	<0.001	10.7	0.9	<0.001	6.3	0.9	<0.001	5.9	0.8	<0.001
Men														
Stratum 1[*]														
<6.5	51,984	349.8 ± 73.2	9.0	0.6	<0.001	10.5	0.6	<0.001	0.2	0.6	0.80	0.8	0.6	0.19
≥6.5	3551	341.3 ± 79.4	−8.4	0.5	<0.001	−8.6	0.5	<0.001	−8.7	0.5	<0.001	−7.1	0.5	<0.001
Difference between 2 stratums			17.4	0.8	<0.001	19.1	0.8	<0.001	9.4	0.8	<0.001	8.6	0.8	<0.001
Stratum 2														
<7.0	53,375	350.0 ± 73.3	8.3	0.6	<0.001	9.8	0.6	<0.001	−0.5	0.6	0.42	0.3	0.6	0.54
≥7.0	2160	330.1 ± 80.6	−7.9	0.6	<0.001	−8.2	0.6	<0.001	−7.0	0.6	<0.001	−6.2	0.6	<0.001
Difference between 2 stratums			16.1	0.8	<0.001	17.9	0.8	<0.001	7.9	0.8	<0.001	7.3	0.8	<0.001
Difference between 2 genders														
Women < 7.5 vs men < 6.5			1.7	0.8	0.04	1.5	0.8	0.07	1.3	0.8	0.10	1.0	0.8	0.21
Women ≥7.5 vs men ≥ 6.5			3.9	1.2	<0.001	3.9	1.2	<0.001	3.8	1.1	<0.001	3.7	1.1	<0.001
Women < 7.0 vs men < 7.0			2.2	0.8	0.006	2.1	0.8	0.01	1.7	0.8	0.02	1.2	0.8	0.12
Women ≥7.0 vs men ≥ 7.0			3.4	1.1	0.002	3.5	1.1	0.001	3.0	1.0	0.004	3.0	1.0	0.003

FPG = fasting plasma glucose, SE = standard error, UA = uric acid.
[*]Threshold effect analysis of FPG on UA using piece-wise linear regression.
[†]No adjustment.
[‡]Adjustment for age.
[§]Additional adjustment for body mass index, diastolic blood pressure, systolic blood pressure, total cholesterol, triglycerides, drinking status, and smoking status.
[∥]Further adjustment for estimated glomerular filtration rate.

UA is the metabolic end-product of purine metabolism in humans because of uricase loss. The generated and excluded volumes of UA affect its level in blood. Serum UA level could increase because of increase in its production, decrease in its excretion, or both. Increase in insulin levels (hyperinsulinemia and insulin resistance) could lead to enhancement of tubular sodium reabsorption.[24] Tubular sodium reabsorption will decrease excretion of UA, followed by increase in the serum level of UA. In addition, the activity of xanthine dehydrogenase and purine nucleoside phosphorylase, which participate in UA synthesis, may increase because of insulin, thus elevating the serum level of UA.[25] Interference with glycolysis would redirect metabolite flow through the hexose–monophosphate pathway, followed by increase in the production of UA.[26]

It is argued that the low level of UA in the serum in diabetes is due to changes in renal handling instead of decrease in the production of UA.[27] UA is completely filtered in the renal glomeruli and is almost completely reabsorbed in the proximal tubule. Increase in the urine level of glucose will lead to competitive inhibition of reabsorption of UA; furthermore, this increase will enhance the excretion of UA.[23,28–31] The elevation in eGFR and hyperfiltration in diabetes, particularly in the early stage of the disease,[32] appears to be another potential mechanism, as a negative association has been noted between eGFR

and the level of UA.[33,34] In our results, after adjusting for eGFR, these associations were moderately attenuated, which suggested that the association between FPG and serum UA is partly mediated through eGFR and hyperfiltration. Furthermore, in diabetes, oxidant stress may play an important part in the relationship between UA and FPG, as suggested in many recent studies.[35,36] Oxidant stress could precede endothelial dysfunction and occurs in cases where there is a moderate increase above the normal FPG level.[36] Another possible explanation for lower UA levels in diabetes is the renal SLC2A9 (GLUT9) transporter, which is known to reabsorb glucose in exchange for excretion of UA.[37] This potential mechanism is supported by evidence of trans-stimulation of UA efflux with high glucose concentration in *Xenopus oocytes* expressing SLC2A9b.[38] Notably, the identification of the stage and duration of diabetes mellitus is an important factor in that relationship, so this study excluded patients with known diabetes.

Nevertheless, the reasons for the differential threshold of FPG between genders are still not clear. One reason may be that the serum UA and eGFR in women are lower than it in other subpopulation. As mentioned before, the association between FPG and serum UA is partly mediated through eGFR and hyperfiltration, and considering the effect of FPG on UA may have a threshold effect and saturation effect, thus the
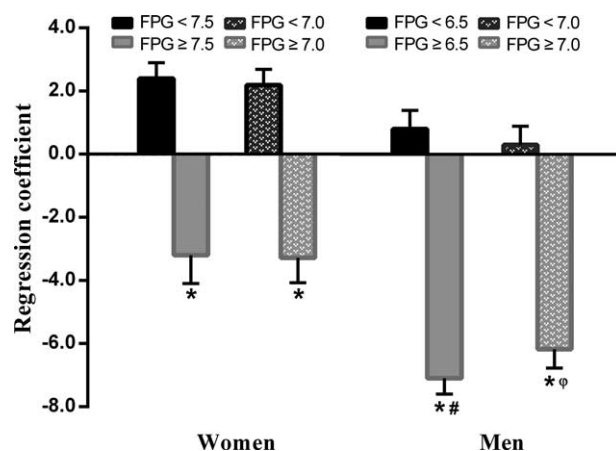
FIGURE 2. Regression coefficients (β) and their standard error of fasting plasma glucose (mmol/L) on serum uric acid concentration (μmol/L) using piece-wise linear regression. Model adjustment for age, body mass index, diastolic blood pressure, systolic blood pressure, total cholesterol, triglycerides, drinking status, smoking status, antihypertensive treatment status, and estimated glomerular filtration rate. FPG = fasting plasma glucose, mmol/L. [*]$P < 0.001$, compare with relative stratum among same gender, respectively. [#]$P < 0.001$, compare with participants with FPG ≥ 7.5 mmol/L in women. [φ]$P = 0.003$, compare with participants with FPG ≥ 7.0 mmol/L in women.

threshold value of FPG in woman is higher than man. Besides, differential findings of regression coefficient between genders are interesting (Table 2). Unfortunately, the different findings by genders cannot be explained now. Many questions about this point should be addressed before any conclusion could be reached. The deeper researches to explore the mechanisms underlying this relationship in the future are needed.

The advantage of the present study is using epidemiological investigation with a large sample size, which has sufficient effectiveness. Considering the 100,348 healthy Wuhu citizens presenting for a health check-up reflects the general health community population, our study population was a representative sample of central and southern Anhui, China. In addition, all of blood biochemical examinations were finished in the same institution, which ensures the stability and accuracy of the examined data. What is undeniable is that our study was cross-sectional. Therefore, the temporal nature of the association between FPG and UA cannot be established from present study. The other limitation of our study is that the 2-h oral glucose tolerance test (OGTT) was not conducted and the diabetes status of participants was defined with the FPG. Although the 75-g OGTT is more sensitive than the FPG in diagnosing diabetes, it is difficult to perform in practice. A previous study[14] has found that the relationship between UA and 2-h blood glucose level was not as strong as that for FPG. In addition, some potential confounding factors such as seafood consumption, C-reactive protein, fasting insulin, ApoA, ApoB, and taking aspirin or diuretics were not available. Nevertheless, considering the seafood consumption remains low in Chinese inland, few people taking aspirin or diuretics, and some other important confounding factors have been adjusted, those potential confounding may not have a great influence on our results.

In summary, an invert U-shaped relationship was observed between the FPG and serum UA concentration in individuals without known diabetes, and there were significant differences considering genders. It probably reflects the biochemical

interaction between serum glucose and purine metabolism. Future researches should consider the influence of glycemia and gender differences when studying UA role in relevant diseases or the UA-lowering therapies, and the uricosuric effect of glycemia cannot be ignored.

REFERENCES

1. Lehto S, Niskanen L, Ronnemaa T, et al. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke.* 1998;29:635–639.

2. Newman EJ, Rahman FS, Lees KR, et al. Elevated serum urate concentration independently predicts poor outcome following stroke in patients with diabetes. *Diabetes Metab Res Rev.* 2006;22:79–82.

3. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum.* 2009;61:885–892.

4. Hu G, Sarti C, Jousilahti P, et al. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke.* 2005;36:2538–2543.

5. Chou YC, Kuan JC, Yang T, et al. Elevated uric acid level as a significant predictor of chronic kidney disease: a cohort study with repeated measurements. *J Nephrol.* 2015;28:457–462.

6. Athyros VG, Mikhailidis DP. Uric acid, chronic kidney disease and type 2 diabetes: a cluster of vascular risk factors. *J Diabetes Complications.* 2014;28:122–123.

7. Gerber Y, Tanne D, Medalie JH, et al. Serum uric acid and long-term mortality from stroke, coronary heart disease and all causes. *Eur J Cardiovasc Prev Rehabil.* 2006;13:193–198.

8. Yamamoto-Honda R, Ehara H, Kitazato H, et al. The long-term coronary heart disease risk of previously obese patients with type 2 diabetes mellitus. *BMC Endocr Disord.* 2013;13:38.

9. Culleton BF, Larson MG, Kannel WB, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med.* 1999;131:7–13.

10. Oda E, Kawai R, Sukumaran V, et al. Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men. *Intern Med.* 2009;48:1785–1791.

11. Whitehead TP, Jungner I, Robinson D, et al. Serum urate, serum glucose and diabetes. *Ann Clin Biochem.* 1992;29 (Pt 2):159–161.

12. Tuomilehto J, Zimmet P, Wolf E, et al. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am J Epidemiol.* 1988;127:321–336.

13. Hairong N, Zengchang P, Shaojie W, et al. Serum uric acid, plasma glucose and diabetes. *Diab Vasc Dis Res.* 2010;7:40–46.

14. Nan H, Dong Y, Gao W, et al. Diabetes associated with a low serum uric acid level in a general Chinese population. *Diab Res Clin Pract.* 2007;76:68–74.

15. Meisinger C, Doring A, Stockl D, et al. Uric acid is more strongly associated with impaired glucose regulation in women than in men from the general population: the KORA F4-study. *PLoS ONE.* 2012;7:e37180.

16. Herman JB, Goldbourt U. Uric acid and diabetes: observations in a population study. *Lancet.* 1982;2:240–243.

17. Cook DG, Shaper AG, Thelle DS, et al. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J.* 1986;62:1001–1006.

18. Gill A, Kukreja S, Malhotra N, et al. Correlation of the serum insulin and the serum uric acid levels with the glycated haemoglobin levels in the patients of type 2 diabetes mellitus. *J Clin Diagn Res.* 2013;7:1295–1297.

19. Safi AJ, Mahmood R, Khan MA, et al. Association of serum uric acid with type 2 diabetes mellitus. *JPMI.* 2004;18:59–63.

20. Yu Y, Jiang C, Jin Y, et al. Association between serum uric acid and fasting plasma glucose in middle and elderly Chinese. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2014;35:1155–1159.

21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.

22. Anderson-Cook CM. Generalized additive models: an introduction with R. *J Am Stat Assoc.* 2007;102:760–761.

23. Magoula I, Tsapas G, Paletas K, et al. Insulin-dependent diabetes and renal hypouricemia. *Nephron.* 1991;59:21–26.

24. Bonora E, Capaldo B, Perin PC, et al. Hyperinsulinemia and insulin resistance are independently associated with plasma lipids, uric acid and blood pressure in non-diabetic subjects. The GISIR database. *Nutr Metab Cardiovasc Dis.* 2008;18:624–631.

25. Wu JM, Nickels JS, Fisher JR. Regulation of nitrogen catabolic enzymes in chick liver: effects of insulin. *Enzyme.* 1977;22:60–69.

26. Facchini F, Chen YD, Hollenbeck CB, et al. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA.* 1991;266:3008–3011.

27. Golembiewska E, Ciechanowski K, Safranow K, et al. Renal handling of uric acid in patients with type 1 diabetes in relation to glycemic control. *Arch Med Res.* 2005;36:32–35.

28. Gotfredsen A, McNair P, Christiansen C, et al. Renal hypouricaemia in insulin treated diabetes mellitus. *Clin Chim Acta.* 1982;120:355–361.

29. Erdberg A, Boner G, van Dyk DJ, et al. Urine uric acid excretion in patients with insulin-dependent diabetes mellitus. *Nephron.* 1992;60:134–137.

30. Golik A, Weissgarten J, Cotariu D, et al. Renal uric acid handling in non-insulin-dependent diabetic patients with elevated glomerular filtration rates. *Clin Sci (Lond).* 1993;85:713–716.

31. Shichiri M, Iwamoto H, Shiigai T. Diabetic renal hypouricemia. *Arch Intern Med.* 1987;147:225–228.

32. de Boer IH, Sun W, Cleary PA, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med.* 2011;365:2366–2376.

33. Kanda E, Muneyuki T, Kanno Y, et al. Uric acid level has a U-shaped association with loss of kidney function in healthy people: a prospective cohort study. *PLoS ONE.* 2015;10:e0118031.

34. Chen Z, Ding Z, Fu C, et al. Correlation between serum uric acid and renal function in patients with stable coronary artery disease and type 2 diabetes. *J Clin Med Res.* 2014;6:443–450.

35. Gopaul NK, Manraj MD, Hebe A, et al. Oxidative stress could precede endothelial dysfunction and insulin resistance in Indian Mauritians with impaired glucose metabolism. *Diabetologia.* 2001;44:706–712.

36. Konukoglu D, Dogan E, Turhan MS, et al. Impaired glucose tolerance: its relevance to early endothelial dysfunction. *Horm Metab Res.* 2003;35:607–610.

37. Caulfield MJ, Munroe PB, O'Neill D, et al. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med.* 2008;5:e197.

38. Chino Y, Samukawa Y, Sakai S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos.* 2014;35:391–404.